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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/416,812	10/13/99	RAMACHANDRA M	CJ-0926KUS

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EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1633	3

DATE MAILED: 01/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/416,812	Applicant(s) Ramachandra et al
	Examiner Yvette Connell Albert	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-40* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 is rejected under 35 U.S.C. 112 second paragraph as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 provides for the use of a diagnostic kit of parts containing a selectively replicating virus and a transgene expression cassette containing a reporter gene with appropriate instructions for use, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 37 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example Ex parte Dunki, 153 USPQ 678 (Bd.App. 1967) and Clinical Products, Ltd. v. Brenner, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

only pharmaceutical 14-28 formulations 30-36 method of killing cells

Claims 14 -36 are rejected under 35 U.S.C. 112 first paragraph, because the specification while being enabling for an *in vitro* method of utilizing a selectively recombinant adenoviral vector comprising a pathway-responsive promoter such as p53, TGF-beta or RB promoter operably linked to a repressor of viral replication such as E2F-RB, and the specification while being enabling for a method of making a selectively replicating viral vector by infecting producer cells such as 293 cells and A549 cells, fails to provide enablement for the *in vivo* method of treating any cancer by a pharmaceutical formulation administered to a subject; or a method of killing a cell with a pathway defect by contacting the target cell with a selectively replicating recombinant adenovirus comprising a pathway-responsive promoter operably linked to a repressor of viral replication, to eliminate tumor cells from stem cells. The specification does not enable any person skilled in the art to which it pertains, or to which it is most nearly connected, to make and or use the invention in scope with these claims.

1. Claimed invention. The claims are drawn to pharmaceutical formulations and a method of killing cells with regulatory pathway defects, via a selectively recombinant adenoviral vector comprising pathway-responsive promoters linked to a repressor of viral replication. The specification considers the instant invention to be applied for the treatment of diseases associated with uncontrolled cellular proliferation such as neoplasms, especially malignant neoplasms or cancers or tumors. The claims are broadly drawn to a pharmaceutical formulation comprising a selectively replicating recombinant adenoviral vector, comprising any pathway-responsive promoter operably linked to any repressor of viral replication. Additionally, the pharmaceutical formulation claims imply a method of treatment and in vivo gene therapy, as well as the method claims thereof.

Cancer is a genetic disease wherein carcinogenesis involves a multistage process involving multiple genetic and epigenetic events in proto-oncogenes, tumor suppressor genes, and antimetastasis genes. Chemicals, radiation, and viruses can all contribute to cellular transformation by attacking genetic material and activating proto-oncogenes or inactivating tumor suppressor genes. The initiated cells can expand themselves and their defects by showing dysregulated terminal differentiation, lost control of growth, and acquired resistance to cytotoxic effects. This expansion leads to preneoplastic lesions, which progresses further through the process of epigenetic influence and genetic disorder and finally reach the stage of clinical cancer. (Zhang et al, 1995). In the instant invention, applicant is claiming a method whereby malignant neoplastic cells in a mammalian organism can be ablated, in vivo, by the administration of a pharmaceutically acceptable formulation of the recombinant adenovirus of the present invention. Applicant is therefore claiming a method whereby any and all tumor cell types can be killed in which the p53 or TGF-beta or RB regulatory pathways of the cell are defective, by contacting the target cell with a selectively replicating vector of the present invention.

2. The in vitro examples and results on pages 13-16, shows that applicant was successful in producing the TGF-beta pathway responsive promoters by incorporating sequences from plasminogen activator inhibitor-1(PAI-1 promoter) or binding sites for Smad4/DPC4 (SRE-promoter) upstream of SV40 TATA box. The results demonstrate that the PAI and SRE promoters are active only in cells with a functional TGF-beta signal transduction, as indicated by the luciferase expression. Applicant was also successful in showing the results obtained when PAI promoter operably linked to repressor of viral replication, E2F-Rb, selectively repressed E2 promoter in cells with intact TGF-beta pathway. In addition, applicant indicated that the response elements p53CON and RGC-promoters were active in cells with

functional p53, and the activity of the of the p53 responsive promoter increased in a dose-dependent manner with increasing p53 activity.

The specification teaches only generally, the routes of administration of the pharmaceutical formulation, and delineates the possible carriers which could be used with the formulation to enhance stability, sterility, and deliverability of the therapeutic compound. The specification also discloses a method of preparing the selectively recombinant adenoviral vectors used in the instant invention, as well as the producer cell lines and other cell lines used in the study. The specification pointed out the source of the cells lines, and the conditions under which they were maintained. The specification discloses the transfections involving producer cell line, as well as the reporter/luciferase assays, and how one measured virus-mediated cytopathic effect.

3. However, the specification is not enabling for in vivo application because it fails to specifically identify target cells which could be treated by administration of selectively recombinant viral therapy. Applicant teaches that by the use of various pathway responsive promoter elements, one can target the expression of the virus to any given cell with an intact pathway pg.10. Applicant does not provide guidance of how one would determine whether or not a cell has an intact pathway, or how one would determine the type of mutation present in a specific target cell, or how one would determine in a particular instance, which pathway responsive promoter would be best suited to encode the viral replication repressor to target a specific cell and finally, how one would determine in vivo efficacy of the combined therapy. No mention is made of how much conventional chemotherapeutic agents or treatment regimens, which when combined with the recombinant adenoviruses of the present invention, would be therapeutically effective in treating or preventing a particular neoplasm.

The specification fails to provide an enabling disclosure as no teachings are present in terms of effective dosage of selective recombinant adenoviral vector particles to be used in the pharmaceutically acceptable formulation of the instant invention. No mention is made of how many selective recombinant adenoviral particles would be needed per target cell type, or whether or not this dosage would fluctuate depending upon the pathway responsive promoter used, or whether specific tumor cell types would require higher multiplicity of infections, and whether increasing selective recombinant adenoviral particle production would be more or less labor intensive as outlined in the specification.

Retroviral vectors are biological agents which require a greater deal of experimentation to manufacture. They can only be made by living cells, as such, biological systems are unpredictable systems in which to carry out good manufacturing practices (GMP) and quality assurance and quality control (QA/QC) procedures. (Anderson, pg.26, 1998).

The specification fails to provide an enabling disclosure as no teachings are present which would guide the skilled artisan with any degree of specifics in the construction of the pathway responsive promoters mentioned on pages 12-15. It should be noted that the isolation of promoter regions is an unpredictable field requiring extensive experimental practice in order to identify particular transcriptional regulatory regions. The pathway responsive promoters which facilitate the transcription of the viral replication repressor, must also mediate cell type specific transcription and be absolutely specific in its mediation of transcription when introduced into a subject. The specification teaches a limited number of such vectors, but the claims are broadly drawn to encompass such promoters of any origin. It is not readily apparent where a skilled artisan would find such promoters other than disclosed.

The specification fails to provide an enabling disclosure because no mention is made of how one would have constructed the selective recombinant adenoviral vector with the deletions in the E1a region.

Neither is information given in terms of the plasmids used to construct the vector, how the recombinants would have been purified and titered before use. Furthermore, no guidance is given in terms of the experimental conditions required to co-transfect the E2F-RB under the control of either the TGF-beta or p53 pathway responsive promoters, in conjunction with the gene encoding green fluorescent protein used as the reporter in the recombinant adenoviral vector.

On page 17 of the specification, it is noted that cell type specificity or cell type targeting may also be achieved in vectors derived from viruses having characteristically broad infectivities such as adenovirus by the modification of the viral envelope proteins. However, the specification is not enabling as applicant fails to provide experimental conditions or protocols of how to successfully modify the viral genome to achieve expression of viral envelope having specific interaction with unique cell surface receptors.

The specification fails to provide an enabling disclosure because no mention is made of the amounts of pro-drug and antitumor immunosuppressant such as 5-fluorocytosine and MIP-3-alpha respectively, which when administered in conjunction with the recombinant adenovirus and the pathway responsive promoters linked to the viral repressor, would be effective in killing tumor cells, yet aid in developing antitumor immunity in a subject. No evidence is provided which would lead one to conclude that the combination therapy kills tumor cells effectively, yet fosters antitumor immunity in a subject, and no guidance is provided as to how one would have assayed in vivo, to ensure that the combination therapy would have been therapeutically effective.

The specification teaches immunological response is significant to repeated in vivo administration of viral vectors, and teaches the use of immunosuppressants to be administered in combination with the vectors of the present invention. The applicant while cognizant of this fact by suggesting the co-administration of immunosuppressants, fails to teach how much immunosuppressants, administered how

often to an individual would be sufficient to prevent an immune response associated with viral vector transduction, hence the specification is not enabling in its disclosure. The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. In addition, the immune system is designed to recognize and eliminate foreign gene products and cells that produce a foreign protein. The immune system is still likely to recognize a new or modified protein produced by the therapeutic gene; a newly synthesized normal protein will appear abnormal to an immune system that has never been exposed to it. (Anderson, pg 25, 26, 1998).

The specification provides a method of ablating neoplastic cells by ex vivo transduction. However, no guidance is provided which would allow the artisan to determine how many transfectants would be needed to achieve a "3 log purge or most preferably, a 5 log purge".

The specification fails to provide an enabling disclosure for the delivery of ex vivo transduced cells to the subject. No mention is made as to how many cells would be administered, and the frequency of administration. In addition, no guidance is given as to how one would have separated the stem cells from its tumor cell products, and how the cells would have been reintroduced into the subject.

The specification fails to provide an enabling disclosure for the use of PCR to amplify the desired nucleic acid (primer) sequence by failing to give the experimental conditions under which this PCR would have taken place, how the primers were selected and manufactured, and under what experimental conditions digestion and ligation of the PCR product occurred.

4. The physiological art of utilizing a recombinant adenovirus vector encoding a transgene such as p53 gene to treat cancer as in the instant invention, was well established and yielded excellent results as demonstrated by Song et al, 1997 and Ogawa et al, 1997. However, a selectively replicating recombinant

adenoviral vector comprising a pathway-responsive promoter operably linked to a repressor of viral replication, as a pharmaceutical formulation in a pharmaceutically acceptable carrier, used in the treatment of cancer in an individual, at the time of filing, is considered to be unpredictable.

At the time of filing, there was no confirmed success in any human gene therapy trial, including trials involving a method of ablating neoplastic cells in a mammalian organism in vivo by the administration of a pharmaceutically acceptable formulation of a recombinant adenovirus such as per instant invention. W. French Anderson (Nature 392 S, 25-30, 1998) teaches that: "the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make". At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art via adenoviral vector delivered transgenes and further where cancer can be ameriolated via expression of the transgene.

5. In the absence of specific guidance, and relevant in vivo working examples, and given the state of the art at the time of filing, coupled with the reasons as discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods or use the claimed products as disclosed in the specification.

The quantity of experimentation involved in determining in vivo target cells which have pathway defects, and then selectively killing these cells by the recombinant virus, the lack of guidance regarding the quantity of recombinant virus to be administered for therapy, and which when combined with any pathway responsive promoter, in addition to the standard chemotherapy, radiation and surgery, presents

innumerable variables and as such requires undue experimentation, for one skilled in the art to treat or prevent cancer via adenoviral vector transduction and expression of the transgene.

In addition, the specification requires undue experimentation in determining how to construct the pathway responsive promoters, how to construct the adenoviral vector with the appropriate deletions, how to produce high titers of the adenoviral vectors, and how to determine how much of each component of the pharmaceutical formulation which when added would render the formulation pharmaceutically effective. Hence, the specification while being enabling for the recombinant adenoviral vector production from 293 and A549 cells, fails to provide enablement for the treatment of any neoplastic diseases in an individual in the instant invention, for reasons as discussed above.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

January 7, 2000

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

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